Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial

The Eclampsia Trial Collaborative Group*

Summary
Eclampsia, the occurrence of a seizure in association with pre-eclampsia, remains an important cause of maternal mortality. Although it is standard practice to use an anticonvulsant for management of eclampsia, the choice of agent is controversial and there has been little properly controlled evidence to support any of the options. 1687 women with eclampsia were recruited into an international multicentre randomised trial comparing standard anticonvulsant regimens. Primary measures of outcome were recurrence of convulsions and maternal death. Data are available for 1680 (99·6%) women: 453 allocated magnesium sulphate versus 452 allocated diazepam, and 388 allocated magnesium sulphate versus 387 allocated phenytoin. Most women (99%) received the anticonvulsant that they had been allocated.

Women allocated magnesium sulphate had a 52% lower risk of recurrent convulsions (95% CI 64% to 37% reduction) than those allocated diazepam (60 [13·2%] vs 126 [27·9%]; ie, 14·7 [SD 2·6] fewer women with recurrent convulsions per 100 women; 2p=0·00001). Maternal mortality was non-significantly lower among women allocated magnesium sulphate. There were no significant differences in other measures of serious maternal morbidity, or in perinatal morbidity or mortality. Women allocated magnesium sulphate had a 67% lower risk of recurrent convulsions (95% CI 79% to 47% reduction) than those allocated phenytoin (22 [5·7%] vs 66 [17·1%]; ie, 11·4 [SD 2·2] fewer women with recurrent convulsions per 100 women; 2p=0·00001). Maternal mortality was non-significantly lower among women allocated magnesium sulphate. Women allocated magnesium sulphate were also less likely to be ventilated, to develop pneumonia, and to be admitted to intensive care facilities than those allocated phenytoin. The babies of women who had been allocated magnesium sulphate before delivery were significantly less likely to be intubated at the place of delivery, and to be admitted to a special care nursery, than the babies of mothers who had been allocated phenytoin.

There is now compelling evidence in favour of magnesium sulphate, rather than diazepam or phenytoin, for the treatment of eclampsia.

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Introduction
Eclampsia is defined as the occurrence of one or more convulsions in association with the syndrome of pre-eclampsia. Pre-eclampsia is a multisystem disorder that is usually associated with raised blood pressure and proteinuria. In Europe and other developed countries eclampsia complicates about 1 in 2000 deliveries, while in developing countries estimates vary widely, from 1 in 100 to 1 in 1700. Over half a million women die each year of pregnancy-related causes, and 99% of these deaths occur in the developing world. Although rare, eclampsia probably accounts for 50 000 maternal deaths a year worldwide. In areas where maternal mortality is very high, infection and haemorrhage are the main causes of death, but as deaths from these causes become less common, those associated with hypertension and eclampsia assume greater importance. In the UK, eclampsia is a factor in 10% of direct maternal deaths. Successful prevention of all cases of eclampsia is likely to be difficult; therefore it is important to assess the relative merits of alternative treatments for eclampsia.

Standard practice is to use anticonvulsants to control the immediate fit and prevent further seizures, but the choice of anticonvulsant is controversial. Indeed the debate about which anticonvulsant is most appropriate has been described as "vociferous, if not vitriolic." Currently, the most widely used anticonvulsants are magnesium sulphate, diazepam, and phenytoin.

Magnesium sulphate for this purpose was first suggested in 1906, and has been popular for over 60 years in the USA. It has been advocated in other countries, but in the UK only 2% of obstetricians say they have used it. How might magnesium sulphate act as an anticonvulsant? Plausible suggestions are that it causes vasodilation with subsequent reduction of cerebral ischaemia or blocks some of the neuronal damage associated with ischaemia. Unlike magnesium sulphate, diazepam is widely used for control of other types of seizures. It is simple to administer, cheap, and easily available—factors that, in the 30 years since its introduction, have contributed to its continuing popularity for management of eclampsia in both developed and developing countries. More recently, phenytoin has been advocated for eclampsia on the basis of proven efficacy for other types of convulsions and the lack of sedative effect.

There is little properly controlled evidence about the differential effects of anticonvulsants in eclampsia. A systematic search for relevant randomised trials yielded two studies into which a total of only 73 women had been entered. The first compared magnesium sulphate with diazepam: 51 women were randomised and the results tended to favour magnesium sulphate, although none of the differences were statistically significant. The second trial compared magnesium sulphate with phenytoin, and...
was stopped early when 4 of the 11 women allocated phenytoin had further convulsions while none of the 11 allocated magnesium sulphate did. Since then, two further trials comparing magnesium sulphate with phenytoin for 152 women with pre-eclampsia have included 3 women with eclampsia. In one other trial, 90 women with eclampsia were randomised to receive either magnesium sulphate or lytic cocktail (pethidine/promethazine/chlorpromazine). The Collaborative Eclampsia Trial reported here was designed to estimate more reliably the differential effects of anticonvulsants commonly used for the care of women with eclampsia (magnesium sulphate, diazepam, and phenytoin).

**Patients and methods**

At each collaborating centre the clinicians chose which (of the three) anticonvulsants to compare. As a result of current practice and attitudes in these centres, this resulted in there being two comparisons: magnesium sulphate versus diazepam, and magnesium sulphate versus phenytoin. Overall, 1687 women were randomised. For the comparison of magnesium sulphate versus diazepam recruitment began in July, 1991, and 910 women were randomised at twenty-three centres in eight countries (Argentina, Brazil, Colombia, Ghana, India, Uganda, Venezuela, and Zimbabwe). For the comparison of magnesium sulphate versus phenytoin recruitment opened in January, 1992, and 777 women were randomised at four centres in South Africa and India.

Overall coordination of the trial was from the Perinatal Trials Service (PTS) at the National Perinatal Epidemiology Unit (NPEU) in Oxford, with centres in Argentina, Colombia, and Venezuela coordinated by the Centro Rosarino de Estudios Perinatales (CREP) in Rosario, Argentina. Data analysis was conducted at the PTS. The protocol was approved by local and World Health Organization research/ethics committees. An independent data monitoring committee reviewed unblinded interim data twice in 1993 but found no reason to recommend modification of the trial.

**Trial procedures**

All women with a clinical diagnosis of eclampsia were eligible for trial entry irrespective of when or where the fits had occurred, whether the pregnancy was singleton or multiple, whether the baby had been delivered, or whether anticonvulsant treatment had already been used. The only exclusion criterion was if one of the study drugs that might be allocated in a particular centre was judged to be contraindicated. Follow-up was until death, discharge from hospital, or 6 weeks from trial entry (whichever came first). If a woman was discharged undelivered, data were to be collected later about delivery and outcome for the baby. It was also decided to collect data on any women who had eclampsia but had not been randomised.

Within each comparison, women were allocated to an anticonvulsant regimen by opening the next in a consecutively numbered series of sealed treatment packs. Randomisation was in a ratio of 1:1 within balanced blocks of 2-6 stratified by centre, by means of a customised computer program (at the PTS). Treatment packs were prepared for centres in South America at CREP in Rosario, Argentina; for centres in Kumasi and Kampala at the PTS in Oxford; and for other centres (Harare, Bombay, and the four centres comparing magnesium sulphate with phenytoin) locally by someone not directly involved in recruitment (using randomisation lists, labels, and detailed instructions supplied from PTS). Once the packs had been prepared, the copies of the randomisation lists they used were destroyed, returned to Oxford, or kept locally in a secure place.

The treatment packs were identical in size, shape, weight, and feel and were securely sealed after preparation. Inside each pack was a flow chart outlining how to administer the allocated anticonvulsant, as well as a more detailed description of the treatment regimen. All packs contained sufficient anticonvulsant for the loading dose, for 24 hours' maintenance therapy (plus an additional tapering dose for diazepam), and for treatment of one recurrent convolution. Magnesium sulphate packs also contained 1 g calcium gluconate, in case of magnesium toxicity. When necessary, ballast was included in the packs to ensure there was no detectable difference in weight. For centres comparing magnesium sulphate versus diazepam the packs also contained everything required to initiate therapy (such as needles, syringes, 500 mL normal saline, and an intravenous cannula). At the other centres the clinicians decided it was unnecessary to include these materials.

To enter a woman into the trial the label on the pack lid had first to be completed with the date, time, the woman's name and blood pressure, and whether the baby had been delivered. Only then was the pack to be opened and the allocated anticonvulsant given. Once the label had been completed the woman was considered to have been randomised into the trial, irrespective of whether the box was opened or whether the allocated anticonvulsant was given. All centres were encouraged to report details of recruitment to the coordinating centres as frequently as possible (and at least once a month). If a box was opened out of order or the reported treatment was not consistent with the allocation, this was discussed with the local coordinator to clarify the reason and to plan how to avoid the same thing happening again.

**Treatment regimens**

The treatment regimens chosen for the study were those that are currently recommended and are in clinical use (see below). For some centres where magnesium sulphate was compared with diazepam, anticonvulsant therapy was initiated by either a midwife or a doctor; in other centres the drugs were administered only by doctors.

**Magnesium sulphate therapy** Magnesium sulphate was to be given as an intravenous loading dose, followed for 24 h by either an intravenous infusion or regular intramuscular injections. The intramuscular regimen was that described by Pritchard and colleagues: a loading dose of 4 g intravenously (iv) over 5 min was to be followed by 5 g into each buttok intramuscularly (im), with a further 5 g im every 4 h (provided the respiratory rate was >16/min, urine output >25 mL/h, and knee jerks were present). The intravenous regimen was as described by Zuspan: a loading dose of 4 g iv in most centres, other than those in South America which used a loading dose of 5 g, to be followed by an infusion of 1 g/h for 24 h. For both the intramuscular and intravenous regimens, a further 2–4 g was given iv over 5 min if convulsions recurred. If magnesium sulphate was already in use at a centre, maintenance administration within the trial was to be by the route already used; in those centres where magnesium sulphate was a new treatment, the intramuscular regimen was to be used.

**Diazepam therapy** Diazepam was to be given according to the regimen described by Lean and co-workers and Crowther. A loading dose of 10 mg iv over 2 min, repeated if convulsions recurred, was to be followed by an intravenous infusion of 40 mg in 500 mL normal saline for 24 h. The rate of infusion was titrated against the level of consciousness, with the aim of overcoming restlessness and keeping the woman sedated but rousable. During the next 24 h an infusion of 20 mg diazepam in 500 mL normal saline was to be given and slowly reduced.

**Phenytoin therapy** Phenytoin is only recommended for prevention of convulsions, so diazepam 10 mg iv was to be given as required for immediate control of seizures. Since there is no consensus about an ideal phenytoin regimen and most published reports recommend varying the dose according to the woman's weight (not practical for emergency situations), this regimen was based on clinical practice at the centre that at the start of the trial had the most experience of using phenytoin. An initial loading dose of 1 g iv by slow infusion over 20 min (with continuous cardiac monitoring) was to be followed by a further 100 mg every 6 h for the next 24 h.
Multiparous
Partty
Multiple pregnancy
Mean (SD) age (yr)
Primiparous
Multiparous
Not known
Multiple pregnancy
Any antenatal care
Medical history*
Epilepsy
Renal disease
Chronic hypertension
Other
Not known
First fit
At home
In trial hospital
Other hospital/in transit
Not known
First fit to entry (h)
<1
1-5
>5
Not known
Prior anticonvulsant
Diazepam
MgSO.
Phenytoin
Other, or combinations
Not known
Prior antihypertensive
Not known
At entry
Diastolic BP >110 mm Hg
Systolic BP >170 mm Hg
Proteinuria
None
1+
2+
3+
Not known
Consciousness
Fully
Sem/unconscious
Not known
Antepartum/intrapartum
Postpartum
Randomised before delivery
Gestation at randomisation (wk)
<34
34-37
>37
Not known
Randomisation after delivery
<24 h after delivery
Gestation at delivery (wk)
<34
34-37
>37
Not known
Deaths
Pentobarbital
After first week
Not known

No (%) in allocated group
MgSO.
Diazepam
Phenytoin
No (%) in allocated group
MgSO.
Diazepam
Phenytoin

Allocated anticonvulsant
447 (99)
444 (98)
386 (99)
382 (99)
Alone
407 (90)
361 (84)
351 (90)
336 (87)
+MgSO.
15
13
21
21
+Diazepam
20
14
8
8
+Phenytoin
5
5
6
6
+Other

No allocated anticonvulsant
6 (1)
8 (2)
1 (2)
5 (1)

*B3 women received diazepam; 1 woman received diazepam; 25 women received diazepam; 48 women received diazepam; 10 women received diazepam.

Table 2: Compliance with allocated anticonvulsant

Outcome measures

The prespecified primary measures of outcome were recurrence of convulsions and maternal death. Secondary measures of outcome were potentially life-threatening events including pulmonary oedema, cardiac arrest, respiratory depression, pneumonia, renal failure, disseminated intravascular coagulation, cerebrovascular accident, and liver failure. Since the number of these events was likely to be small, none were prespecified.

The first was defined as morbidty likely to be directly related to eclampsia (renal failure, liver failure, coagulopathy, or cerebrovascular accident). The second included, in addition, death or other measures of severe morbidity (cardiac arrest, cardiac arrhythmia, pulmonary oedema, need for ventilation, respiratory depression, pneumonia). For women entered into the trial before delivery of the baby, additional measures of outcome were those relevant to labour and delivery, as well as perinatal morbidity and mortality. Outcome was as determined by the attending clinicians. The clinicians knew the allocated treatment, so it was not possible to blind the assessment of outcome. For this reason the measures used to assess outcome were as objective as possible; and, where information was available, causes of maternal death were validated by independent review of either the full case notes or a clinical summary.

Statistical methods

Although maternal mortality is the most important outcome of eclampsia, a difference in the risk of death would be difficult to demonstrate. For example, if the case fatality was halved from 10% to 5% then a trial involving about 800 women would have a power of 80% to detect this difference at the 5% level of significance, but for a halving from 5% to 2.5% the power would only be about 50%. Moreover, differences in maternal mortality considerably smaller than halvings (such as a reduction of 20-30%) would still be of substantial clinical importance. For this reason, it was prespecified that recurrence of eclampsia would be a second primary outcome. If 30% of women in one group had recurrent convulsions, and this was reduced by one-third (ie, to 20%) a trial of about 800 women would have a 90% chance of detecting this difference at the 5% level, and an 80% chance at the 1% level.

Analysis of the primary and secondary measures of outcome was based on the groups as randomly allocated (ie, an intention-to-treat comparison). For the primary measures, statistical significance was taken as the 5% level (with 95% confidence intervals), and for the secondary measures significance was taken as the 1% level (with 99% CI). As prespecified in the trial protocol, subgroup analyses were to be performed among women stratified by whether delivered at trial entry, and whether any anticonvulsant had been given before trial entry. Where appropriate, results are presented as relative risks (with 95% CIs) and as numbers of events prevented (compared with the alternative treatment) per 100 women (with I standard deviation, which can be multiplied by I-96 to give the approximate 95% CI.

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and by 2.58 to give the approximate 99% CI. Means (with standard errors) and medians (with interquartile ranges) are given where appropriate.

Results

Data are available for 905 women (99.5% of the 910 women randomised) in the comparison of magnesium sulphate versus diazepam and 775 women (99.7% of the 777 women randomised) in the comparison of magnesium sulphate versus phenytoin. 7 women have been excluded from this analysis. Packs were opened in error (by staff not familiar with the trial protocol) for 2 women with pre-eclampsia, neither of whom had any serious complication (both had healthy babies). 2 women discharged themselves (taking their case records with them); 1 woman thought to have hysteria rather than eclampsia was discharged undelivered and was lost to follow-up. No data are available for an additional 2 women. 3 women with recurrent fits were randomised twice in the same pregnancy, but in the analysis each has been included once only in the group to which she was first allocated.

2.7% of the packs were not opened in consecutive order. In most cases the reason for this seemed to be human error. Only 55 women with eclampsia were admitted to the participating centres and not randomised, so 97% of eligible women were recruited. Data are available for 53 (96.4%) of the women not recruited, of whom 1 died (1.9%) and 11 had further fits (20.8%).

Magnesium sulphate versus diazepam

In the comparison of magnesium sulphate versus diazepam, the groups generated by randomisation were well balanced in respect of prognostic factors (table 1). At trial entry, 66% of the women were in their first pregnancy, 61% had made at least one antenatal visit, 3% had a multiple pregnancy, 52% had already received an anticonvulsant, 51% had diastolic blood pressure of 110 mm Hg or more, and 30% had delivered. Of the women allocated to magnesium sulphate, 99% actually received it; of these, 9% also had another anticonvulsant (table 2). 98% of those allocated diazepam received it, 14% of whom also had another anticonvulsant (table 2). Only 14 women did not have the anticonvulsant that was originally allocated, either because of errors in preparing the boxes (10) or because of a clinical decision to give a different anticonvulsant (3) or no anticonvulsant (1). For the 229 women allocated to im magnesium sulphate, the mean total dose was 40 g (SD 11.8) and the median was 44 g (interquartile range 39-44 g). For the 224 women allocated iv magnesium sulphate the mean total dose was 24 g (SD 10.7) and the median was 25 g (interquartile range 20-30 g). Mean total dose for women allocated diazepam was 107 mg (SD 59) and the median dose was 90 mg (interquartile range 70-160 mg). The fact that these doses were close to those expected suggests that most women had the regimen described in the protocol.

<table>
<thead>
<tr>
<th>MgSO₄</th>
<th>Diazepam</th>
<th>Relative risk (95% CI)</th>
<th>Absolute reduction/ 100 allocated MgSO₄, mg (SD)</th>
<th>Phenytoin</th>
<th>Relative risk (95% CI)</th>
<th>Absolute reduction/ 100 allocated MgSO₄, mg (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 (3.8%)</td>
<td>23 (5.1%)</td>
<td>0.74 (0.40-1.36)</td>
<td>1.3 (1.4)</td>
<td>10 (2.6%)</td>
<td>20 (5.2%)</td>
<td>0.50 (0.24-1.95)</td>
</tr>
<tr>
<td>1* (0.2%)</td>
<td>1* (0.2%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>60 (13.2%)</td>
<td>126 (27.9%)</td>
<td>0.48 (0.30-0.63)</td>
<td>14.7 (2.6)</td>
<td>22 (5.7%)</td>
<td>66 (17.1%)</td>
<td>0.33 (0.21-0.53)</td>
</tr>
</tbody>
</table>

*Transferred from the collaborating centre to another hospital, and then lost to follow-up.

Table 3: Primary measures of outcome

There were significantly fewer recurrent convulsions among women allocated magnesium sulphate than among those allocated diazepam (60 [13.2%] vs 126 [27.9%]; ie, 14.7 [SD 2.6] fewer women with recurrent convulsions per 100 women; 2p<0.00001) (table 3). This represents a 52% lower risk of further convulsions (95% CI 64% to 37% reduction), and among those who did have recurrent convulsions fewer allocated magnesium had more than one recurrence (figure 1). More women allocated diazepam were given additional anticonvulsant therapy than those allocated magnesium (table 2). The effect on recurrent convulsions appeared to be similar to that observed overall irrespective of whether the women were randomised before or after delivery, and of whether they had been given anticonvulsant therapy before trial entry (figure 2). Maternal mortality was non-significantly lower among women allocated magnesium sulphate (17 [3.8%] vs 23 [5.1%]; 26% lower risk with 95% CI 60% reduction to 36% increase). There were no clear differences between the groups in any other measures of serious maternal morbidity (including the prespecified morbidity indices) or in the use of intensive-care facilities (table 4). 2 women allocated to magnesium sulphate had an abscess at the injection site.

For women randomised before delivery there were no significant differences in the proportion having labour induced or being delivered by caesarean section (table 5).
(i) Magnesium sulphate versus diazepam

<table>
<thead>
<tr>
<th>Entry characteristic</th>
<th>Recurrent convulsion/women</th>
<th>Relative risk and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MgSO₄</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Before delivery</td>
<td>46/325</td>
<td>83/308</td>
</tr>
<tr>
<td>After delivery</td>
<td>14/128</td>
<td>43/144</td>
</tr>
<tr>
<td>No prior anticonvulsant*</td>
<td>33/198</td>
<td>64/218</td>
</tr>
<tr>
<td>Prior anticonvulsant*</td>
<td>25/244</td>
<td>60/227</td>
</tr>
<tr>
<td>All women</td>
<td>60/453</td>
<td>126/452</td>
</tr>
</tbody>
</table>

*Not known whether prior anticonvulsant was given to 11 women allocated MgSO₄ and to 7 allocated diazepam

Figure 2: Effects on recurrent convulsions

Non-significantly more perinatal deaths occurred among those allocated magnesium sulphate than those allocated diazepam (82 [24·8%] vs 71 [22·4%]) (table 5). For babies liveborn after trial entry, the only statistically significant differences in morbidity were for the Apgar score at 1 min, with fewer Apgar scores less than 7 among babies of women allocated magnesium sulphate (49% vs 62%, 2p=0·002), and for length of stay in a special-care baby unit of more than 7 days (12·4% vs 19·5%; 2p=0·04) (table 5).

Magnesium sulphate versus phenytoin

In the comparison of magnesium sulphate versus phenytoin, the groups generated by randomisation were likewise well balanced (table 1). At trial entry, 64% of the women were in their first pregnancy, 64% had made at least one antenatal visit, 3% had a multiple pregnancy, 78% had already received an anticonvulsant, 53% had a diastolic blood pressure of 110 mm Hg or more, and 19% had delivered (table 1). Although slightly fewer of the women randomised before delivery and allocated magnesium sulphate were below 34 weeks’ gestation at entry (36% vs 43%), the proportions of women below 37 weeks were very similar (28% vs 27%) (table 1). Of the women allocated magnesium sulphate 99% actually received it, and of these 9% also received another anticonvulsant (table 2). 99% of those allocated phenytoin received it (12% also received diazepam), 12% of whom had another anticonvulsant. Only 7 women did not have the anticonvulsant that was originally allocated, because of errors in preparing the boxes (3), a clinical decision to give a different anticonvulsant (2) or no anticonvulsant (1), or unfamiliarity with the trial protocol (1). For the 336 women allocated im magnesium sulphate, the mean total dose was 38 g (SD 9·7) and the median was 39 g (interquartile range 34–44 g). For the 52 women allocated iv magnesium sulphate the mean total dose was 29 g (SD 14·9) and the median was 29 g (interquartile range 23–34 g). Mean total dose of phenytoin for women allocated to it was 1376 mg (SD 281) and the median dose was 1400 mg (interquartile range 1400–1400 mg). Mean total dose of diazepam for these women was 2·9 mg. Again, the fact that doses were close to those expected suggests that most women had the regimen described in the protocol.

There were significantly fewer recurrent convulsions among women allocated magnesium sulphate than among those allocated phenytoin (22 [5·7%] vs 66 [17·1%]; ie, 11·4 [SD 2·2] fewer women with recurrent convulsions per 100 women; 2p<0·00001) (table 3). This represents a 67% lower risk of further convulsions (95% CI 79% to 47% reduction), and among those who did have recurrent convulsions fewer allocated magnesium had more than 1 recurrence (figure 1). More women allocated the
The Collaborative Eclampsia Trial was designed to assess the effects on recurrent convulsions and on maternal mortality of different anticonvulsant regimens in widespread use for women with eclampsia. The key principles considered at the design stage were that the results should be generalisable to places where maternal mortality is highest, that the study should be conducted within the existing health services, and that treating a woman within the trial should be faster and easier than outside it so that busy clinicians were not burdened and large numbers of women could be studied. This last objective was intended to ensure that care for women...
within the trial should be at least as good as, if not better than, the care they would have received if they had not been entered. Measures of how successfully these aims were achieved are the low attrition, high compliance, and completeness of data collection.

Almost all women (99%) received the allocated anticonvulsant, and for the few who did not the commonest reason was human error. Not surprisingly, it was the women who had further fits who were most likely to have an anticonvulsant in addition to the one allocated. In both comparisons outcome was best for women allocated magnesium sulphate, with clear and substantial reductions in recurrent fits. In the comparison of magnesium sulphate with diazepam, 15 per 100 fewer women allocated magnesium sulphate had further fits, while in the comparison of magnesium sulphate with phenytoin, 11 per 100 fewer women allocated magnesium sulphate had recurrent convulsions. Despite the inevitable reduction in power of a subgroup analysis, the results were consistent irrespective of whether randomisation was before or after delivery and of whether patients had received anticonvulsants before trial entry. The trends in maternal mortality also favoured magnesium sulphate, although the results could not exclude a slightly higher mortality. Also, in the comparison with phenytoin, 5% fewer women allocated magnesium had pneumonia, 8% fewer needed ventilation, and 8% fewer were admitted to intensive-care facilities. It is possible, however, that these latter differences were due to complications of phenytoin rather than benefits of magnesium sulphate.

For women randomised before delivery, overall 27% of their babies died. In both comparisons, this very high mortality was explained partly by the poor outcome for babies randomised in utero before 34 completed weeks (mortality 49–58%, data not shown). In the comparison of magnesium sulphate with diazepam there were no clear differences in outcome for the baby, whereas in the comparison of magnesium sulphate with phenytoin the babies of women allocated magnesium sulphate did somewhat better. The better outcome of babies in the magnesium group than in the phenytoin group was also reflected in measures of morbidity with, for example, 11% fewer being intubated at the place of delivery and 12% fewer admitted to a special-care nursery. Once again, it is possible that these differences were due to ill-effects of phenytoin rather than benefits of magnesium sulphate.

The only unbiased comparisons in this trial are of magnesium sulphate versus diazepam and of magnesium sulphate versus phenytoin. Comparisons of any other groups within the trial should be interpreted with caution, since they are potentially misleading.

Eclampsia is often regarded as largely a problem for developing countries but it is still associated with a substantial mortality in the developed world. Although this trial was conducted in developing countries, there are several reasons why the results should be considered in determining the care of women with eclampsia in developed countries. First, the only data from developed countries are derived from uncontrolled case series and so are prone to all the misleading biases associated with such studies. Second, the low incidence of eclampsia makes it unlikely that a trial of this size could ever be conducted in developed countries. Third, the reduction in further fits associated with magnesium sulphate (compared with diazepam or phenytoin) is large and consistent in the various subgroups and the different study settings so that, although it may be less in other settings, it is unlikely to change direction. Finally, despite considerable regional variation in incidence, women with eclampsia have surprisingly similar morbidity and mortality wherever they live. If we compare women in this trial with those described in a recent population-based survey of eclampsia in the UK, for example, the levels of maternal morbidity and mortality were similar.

Implications for practice

The use of magnesium sulphate for management of women with eclampsia has been described as "more a matter of habit, if not religious conviction, than a scientifically established treatment." The present study now provides strong support for the routine use of magnesium sulphate rather than either diazepam or phenytoin. Phenytoin appeared particularly ineffective in comparison with magnesium sulphate (with the possibility, even, of increases in requirement for maternal ventilation, pneumonia, and admission to intensive care) and so would not seem justified for the routine management of eclampsia. Diazepam was also less effective than magnesium sulphate at preventing further seizures, although there was no clear evidence of any other disadvantages. Since magnesium sulphate is cheap and easy to produce, its ready availability should be a priority for all those concerned with maternal health, and the essential drug lists of the World Health Organization and other bodies need to be amended accordingly.

Practical advantages of magnesium sulphate are that it is cheaper and easier to administer than phenytoin (for which cardiac monitoring is required), and that subsequent nursing is likely to be easier than for women given diazepam with its sedative properties. These factors also suggest that magnesium sulphate may be appropriate for use at primary health centre level. This trial was not designed to compare different regimens for administering magnesium sulphate. However, there was no evidence of any difference between the intramuscular and intravenous regimens in their effects on recurrent convulsions.

Anticonvulsants are also given to women with severe pre-eclampsia with the aim of preventing the first fit, although whether this does more good than harm is unclear. For those clinicians who do wish to use an anticonvulsant for such women, magnesium sulphate seems at present the most rational choice and the least likely to cause harm.

Implications for future research

This trial presents a model for tackling some of the major problems in women's health in developing countries. It demonstrates that large simple trials conducted within the existing health services can provide reliable evidence about the effects of specific interventions, and at a relatively low cost. Yet, although this study was more than thirty times larger than any previous trial involving women with eclampsia, it would have been even more informative if it had been bigger and had provided clearer evidence about the effects on maternal death.

A major problem for preventing and treating eclampsia is that the pathogenesis of this condition is not known. It has been argued that eclampsia is a seizure like any other seizure, but the present results suggest that this may not be correct. Eclamptic seizures can be distinguished from other sorts of convolution in that they are controlled better by magnesium sulphate than by either diazepam or phenytoin.
The following hospitals (local coordinators) collaborated: South Africa (in total, 677 women randomised)—MRC Pregnancy Hypertension Research Unit, King Edward VIII Hospital, Durban (524 women randomised) (J. Moodley, B. Motshabin); J. S. Strijdom Hospital, Soweto, and Westrand Medical and Reproductive Health Care, Pretoria (R. H. F. Kers), and Lebone Clinic, Soweto (J. J. Schone, C. van Zyl); Kalafong Hospital, Pretoria (50) (G. Haworth, R. Paterson); Argentina (25)—Hospital JRP Vital, Cordem (52) (G. Acosta, E. Mosales, D. Aguirre, J.ailer, J. BIovanno); Hospital Materno Provincial, Cordoba (39) (A. Luco, B. Ortiz, M. Del Car val, R. Riz, E. Mercado Luna); Hospital Posadas, Buenos Aires (43) (M. Palermo, J. Ferreiros, F. Cace, G. Berossi, B. Maschito, R. Lede); Maternidad Provincial de Salta, Salta (25) (M. Casares, S. Paco Lezgo, A. Fallo, A. M0l, A. Sanchez), Maternidad Martin, Rosario (18) (J. Navio, M. Lopez, M. Noblick); Hospital Sanz Peo, Rosario (16) (D. D. Giovanni, C. MacRitchie, A. Jawk, P. Primache, M. Magnin); Hospital Juan D. Peron, Tartagal (12) (D. de Nair); Hospital Eva Peron, Rosario (10) (G. Strada Saenz, J. Larrateb, P. Schlaub, A. Bugnon, V. Ventura); Hospital Cenaniario, Rosario (9) (C. Arenaval, D. Durado, C. Cortez, E. Masa, S. Holli); Hospital Provincial, Rosario (9) (H. Daleno, R. Velasco, D. Fernandez, B. Fiatt, E. Rius); Hospital Fernandez, Buenos Aires (4) (L. Voto, W. Wijsman, A. Lapiton, M. R. Chappell)-Universitario del Valle, Cali (164) (E. Cabo, C. Delgado). Zambia (161)—Harare Maternity, Harare (161) (R. Mahomed, S. Mawazi, T. Mavunduse). Costa Rica (145) (A. Caballero, E. Mejia, D. Mavar, R. Rios); Hospital Juan D. Peron, Rosario (18) (G. George, C. James, N. Balabasramabian, J. Jarper, L. Scabdi); Nowrojee Wadia Maternity Hospital, Bombay (26) (M. Hansoti, N. Sheria); King Edward VII Memorial Hospital, Bombay (23) (S. Sheth, V. Rarae); Venezuela (111)—Maternidad Conception Palacios, Caracas (111) (F. Feres, R. Garcia, L. Torres, G. See); Guzau (110)—Koomo Anickey Teaching Hospital, Nkosi (110) (E. Kwaung), S. Adhav, P. Bawaiah); jamaica (52)—Mulago Hospital, Kampala (52) (F. Munro, J. Lade). Brazil (38)—Faculdade de Medicina de Bonfante, Sao Paulo (15) (M. Rudge, J. Peralta), Maternidade Escola Januario Cicco, UFMR, Natal (12) (H. Nobrega, T. Oliveira, R. Carvalho, E. Pires, E. Coss). Faculdade de Medicina de Jundiai, Sao Paulo (5) (L. Mathai, J. Hiar). Hospital do Jabaquara, Sao Paulo (4) (C. Collas). Casa Maternal e Infantil "Leonel Mendes de Barros", Sao Paulo (2) (T. Durant). W. Angi, Escola Paulina de Medicina, Sao Paulo (coordination) (A. Avalos, E. Salazar).

References

Are long-chain polyunsaturated fatty acids essential nutrients in infancy?

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Summary

We investigated whether the disparity in neural maturation between breastfed and formula-fed term infants could be corrected by the addition of fish oil, a source of docosahexaenoic acid (DHA, 22:6w3), to infant formula. Healthy, term infants were randomised at birth to receive either a supplemented or placebo formula if their mothers had chosen to bottle feed. Breastfed term infants were enrolled as a reference group. Infant erythrocyte fatty acids and anthropometry were assessed on day 5 and at 6, 16, and 30 weeks of age. Visual evoked potential (VEP) acuity was determined at 16 and 30 weeks.

VEP acuities of breastfed and supplemented-formula-fed infants were better than those of placebo-formula-fed infants at both 16 and 30 weeks of age (p<0.001 and p<0.01). Erythrocyte DHA in breastfed and supplemented-formula-fed infants was maintained near birth levels throughout the 30-week study period but fell in placebo-formula-fed infants (p=0.001). Erythrocyte DHA was the only fatty acid that consistently correlated with VEP acuity in all infants at both ages tested. A continuous supply of DHA may be required to achieve optimum VEP acuity since infants breastfed for short periods (<16 weeks) had slower development of VEP than infants receiving a continuous supply of DHA from either breastmilk or supplemented formula. Erythrocyte arachidonic acid (20:4w6) in supplemented-formula-fed infants was reduced below that of infants fed breastmilk or placebo formula at 16 and 30 weeks (p<0.001), although no adverse effects were noted, with growth of all infants being similar.

DHA seems to be an essential nutrient for the optimum neural maturation of term infants as assessed by VEP acuity. Whether supplementation of formula-fed infants with DHA has long-term benefits remains to be elucidated.

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Introduction

Preterm breastfed infants are reported to have advanced neural maturation compared with bottle-fed infants as assessed by electroretinograms, visual evoked potentials (VEP), and psychometric tests. It has been proposed that the higher tissue levels of long-chain polyunsaturated fatty acids (LCPUFA), particularly docosahexaenoic acid (DHA, 22:6w3), reported in breastfed infants may be an important causative factor. Breastmilk contains a range of LCPUFAs, whereas bottle-milk formulae are fortified only with precursor essential fatty acids such as linoleic acid (18:2w6) and α-linolenic acid (18:3w3). There is evidence that formula-fed infants are unable to metabolise their full requirement of LCPUFA from precursors, since they have less DHA and less arachidonic acid (20:4o6) in their erythrocytes than breastfed infants. The absence of LCPUFA from formula may be further exacerbated by inhibition of incorporation of endogenously produced LCPUFA by the high concentrations of linoleic acid currently in most infant formulae.

The main concern about fatty acid nutrition in infancy is in preterm infants, because the rate of brain growth is known to be greatest in the last trimester of pregnancy. However, brain growth continues throughout the first year of life and there is evidence that cerebral DHA concentrations are higher in term infants who were breastfed than in those fed formula. Further,